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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/867,159	LORIA ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-73* is/are pending in the application.

4a) Of the above claim(s) *64-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/1/04 has been entered.

2. Claims 36-73 are pending.

3. Claims 64-73 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 36-63, drawn to an anti-allergic pharmaceutical composition comprising an active agent that read on the species of a specific inhibitor of histamine synthesis are being acted upon in this Office Action.

5. Claim 49 is objected to because "SEQ ID NO : 2" should have been SEQ ID NO: 2.

6. Claim 50 is objected to because "SEQ ID NO : 3, SEQ ID NO : 4, and SEQ ID NO :5" should have been SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO:5.

7. Claim 56 is objected to because "SEQ ID NO : 6" should have been SEQ ID NO: 6.

8. Claim 57 is objected to because "SEQ ID NO : 7" should have been SEQ ID NO: 7.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 36-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an anti-allergic pharmaceutical composition comprising (i) an acarid allergen comprising SEQ ID NO: 2, an acarid allergen encoded by the polynucleotide comprising SEQ ID NO: 1 or at least one peptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 3-5, (ii) at least one antihistamine compound selected from the group consisting of brompheniramine, cetirizine, fexofenadine, cyproheptadine, dexchlorpheniramine, hydroxizine, ketotifen, loratadine, mequitazine, oxotomide, mizolastine, ebastine, astemizole, carbinoxamide, alimemazine, buclizine, cyclizine hydrochloride and doxylamine and optionally with an inhibitor of histamine synthesis tritoqualine and a pharmaceutically acceptable carrier, (2) The said pharmaceutical composition wherein the acarid allergen is a major antigens of acarid of *D. Pteronyssinus* and/or *D. Farinae*, (3) The said pharmaceutical composition wherein the acarid allergen is a cystine protease, (4) The said pharmaceutical composition wherein the allergen is present in an amount of 1 to 1500 μg or 10 to 150 μg; (5) the said pharmaceutical composition wherein the antihistamine compound is present in an amount between 1 and 2000 mg or between 5 and 200 mg, (6) the said pharmaceutical composition wherein the inhibitor of histamine synthesis is present in an amount between 1 and 2000 mg or from 5 to 200 mg, and (8) the said pharmaceutical composition wherein the inhibitor of histamine synthesis is an inhibitor of histidine decarboxylase tritoqualine between 10 and 300 mg and wherein the antihistamine compound is from 5 to 200 mg for treating allergic hypersensitivity by reduction of allergic reaction both on the upstream phase of IgE synthesis and reduction on the downstream phase of histamine synthesis and release in children, infants and adults, **does not** reasonably provide enablement for:

(1) *all* anti-anti-allergic pharmaceutical composition comprising (i) any one or more antihistamine compound, (ii) any one or more inhibitor of histamine synthesis, and optionally (iii) any allergen, any major antigens or mixture of any major antigens of acarids, any major antigen of *D. Pteronyssinus* and/or *D. Farinae*, any allergen is a cystine protease, any allergen is at least any peptide epitope of any cystine protease, any one peptide epitope of a cystine protease of sequence of SEQ ID NO: 2, any allergen is a peptide or a mixture of any peptides such as the ones recited in claim 50, any allergen is natural and is obtained by extraction of the acarids *D. Pteronyssinus* and/or *D. Farinae*. (iv) any isolated nucleotide sequence encoding said allergen, any isolated nucleic acid molecule comprises at least any one polynucleotide sequence encoding

any allergen in an adenoviral vector, any polynucleotide such as the ones recited in claims 55-57 as set forth in claims 36-37, and 41-63,

(2) *all* anti-anti-allergic pharmaceutical composition comprising (i) any antihistamine compound such as the ones recited in claim 38, (ii) any inhibitor of histamine synthesis, and optionally (iii) any allergen or (iv) any isolated nucleotide sequence encoding any allergen (claim 38),

(3) *all* anti-anti-allergic pharmaceutical composition comprising (i) any antihistamine compound, (ii) any inhibitor of histamine synthesis such as any histidine decarbosylase inhibitor, and optionally (iii) any allergen or (iv) any isolated nucleotide sequence encoding any allergen (claim 39),

(4) *all* anti-anti-allergic pharmaceutical composition comprising (i) any antihistamine compound, (ii) an histidine decarbosylase inhibitor such as tritoqualine, and optionally (iii) any allergen or (iv) any isolated nucleotide sequence encoding any allergen (claim 40), and

(5) *all* anti-anti-allergic pharmaceutical composition comprising (i) any antihistamine compound, (ii) any inhibitor of histamine synthesis such as any histidine decarbosylase inhibitor, and optionally (iii) any allergen or (iv) any isolated nucleotide sequence encoding any allergen (claim 39) for "**prevention**" of any allergic hypersensitivity reaction, allergic asthma, allergic rhinitis, atopic and allergic eczema or allergic manifestations in children, in infants, and in adults (claims 61-63). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one major allergen from dust mite of *D. Pteronyssinus* (DP) which is also a cystine protease having the amino acid sequence comprising SEQ ID NO: 2 which encodes by the nucleic acid sequence comprising SEQ ID NO: 1 (page 5). The

specification further discloses three allergen peptides consisting of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3-5 that are derived from the cysteine protease of dust mite D. Pteronyssinus (DP) of SEQ ID NO: 1 and D. Farinae (DF) (See page 6). The specification discloses a pharmaceutical composition comprising (i) allergen peptide mentioned above, (ii) an antihistamine compound such as the ones recited in claim 38 and (iii) tritoqualine which is a histamine synthesis inhibitor and a histidine decarboxylase inhibitor and (iv) a pharmaceutical acceptable vehicle (page 10-11) for induction of tolerance to dust mite and to block the histamine synthesis, which is the terminal phase of allergy.

The specification does not teach how to make and use *any* anti-allergic pharmaceutical composition other than the specific pharmaceutical mentioned above because there is insufficient guidance as to the structure of *any* allergen, *any* major antigens among the undisclosed antigens of acarids without the specific amino acid sequence (SEQ ID NO). Further, there is insufficient guidance as to the structure of any antihistamine, any inhibitor of histamine, and any inhibitor of histidine decarboxylase, much less in vivo working example using any pharmaceutical composition.

Stryer *et al,*of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Whisstock *et al* teach prediction of protein function from sequence and structure is a difficult problem because homologous proteins often have different functions (see abstract, in particular).

Attwood *et al*, teaches that protein function is context-dependent; the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable and knowing structure alone will not inherently tell us function (See figure, entire document).

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities. Fasler *et al*, of record, teach that peptides

derived from house dust mite Der p1 are modified by even a single amino acid substitutions at positions 173, 175, 176, 180 and 181 with alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al* further teach that substituting a neutral amino acid residue such as Asn at position 173 with either a basic Lysine, which is a hydrophobic amino acid residue did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

With regard to "antihistamine compound, inhibitor of synthesis or inhibitor of histidine decarboxylase", the '345 patent, of record, teaches drugs known to block the effects of chemical mediators of the allergic reactions such as antihistamines, are used to control the severity of the allergic symptoms and antihistamines **do not prevent** the allergic reactions or **prevent allergic response** to subsequent allergen exposure (See column 1 line 65 bridging column 2 lines 1-4, in particular). Even if the anti-allergic pharmaceutical composition is limited to the specific allergen comprising SEQ ID NO: 1 and the specific anti-histamine compound, the term "prevention" is problematic because as define by the Webster's II New Riverside University Dictionary, that "to keep from happening or to anticipate or counter in advance". The specification fails to provide guidance as how to select or identify an individual before allergy symptoms begin, how to predict who would or would not get allergy, let alone preventing allergy from happening. Given the unlimited number of undisclosed allergen, major antigen of any allergen, major antigen of acarids, polynucleotide encoding any allergen, antihistamine compound, inhibitor of synthesis or inhibitor of histidine decarboxylase, there is insufficient in vivo working example demonstrating that any composition comprising any antihistamine compound, any histamine synthesis inhibitor and any allergen or polynucleotide encoded any allergen is effective for the prevention of all allergic hypersensitivity reaction, all allergic asthma, atopic and allergic eczema and all allergic manifestations in children, in infants and in adults.

With regard to claims 49-50, the term "of sequence" could be open or close ended. There is insufficient guidance as to which the amino acids to be added to the peptide.

With regard to claim 55, the term "at least one" means there are more than one polynucleotide encoding said allergen comprises a sequence SEQ ID NO: 1. However, there is insufficient guidance as to the structure of the other polynucleotide encoding said allergen.

With regard to claims 56-57, SEQ ID NO: 6 in claim 56 and SEQ ID NO: 7 in claim 57 are primers. Primers do not encode the allergen.

Further, there is insufficient guidance and in vivo working example demonstrating that the claimed pharmaceutical composition wherein the allergen is properly expressed in vivo using the adenoviral vector and without triggering host inflammatory immune response (claims 54-58).

Verma *et al* teach that the inherent difficulties of gene therapy is the inability to deliver genes efficiently to the right type of cell, obtaining sustained expression of the therapeutic protein and without triggering the host immune responses (See page 239, in particular).

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

11. Claims 36-63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *all* allergen, (2) all polynucleotide encoding all allergen, (3) all major antigens or mixture of any major antigens of acarids, (4) all major antigen of *D. Pteronyssinus* and/or *D. Farinae*, (5) all allergen is a cystine protease, (5) all allergen is at least any peptide epitope of any cystine protease, (6) any one peptide epitope of a cystine protease of sequence of SEQ ID NO: 2, (7) any allergen is a peptide or a mixture of any peptides such as the ones recited in claim 50, any allergen is natural and is obtained by extraction of the acarids *D. Pteronyssinus* and/or *D. Farinae*, (8) all polynucleotide comprises at least any one polynucleotide sequence encoding any allergen in an adenoviral vector, and (9) any polynucleotide as forth in claims 56-57 in the claimed anti-anti-allergic pharmaceutical composition as set forth in claims 36-63.

The specification discloses only one major allergen from dust mite of *D. Pteronyssinus* (DP) which is also a cystine protease having the amino acid sequence comprising SEQ ID NO: 2 which encodes by the nucleic acid sequence comprising SEQ ID NO: 1 (page 5). The specification further discloses three allergen peptides wherein the peptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3-5 that are derived from the cysteine protease of dust mite D. Pteronyssinus (DP) of SEQ ID NO: 1 and D. Farinae (DF) (See page 6). The specification discloses a pharmaceutical composition comprising (i) allergen peptide mentioned above, (ii) an antihistamine compound such as the ones recited in claim 38 and (iii) tritoqualine which is a histamine synthesis inhibitor and a histidine decarboxylase inhibitor and (iv) a pharmaceutical acceptable vehicle (page 10-11) for induction of tolerance to dust mite and to block the histamine synthesis, which is the terminal phase of allergy.

Other than the specific allergen or the peptide consisting of the specific amino acid sequence, the specific polynucleotide encoding said allergen, the specific antihistamine compound and/or tritoqualine for the claimed anti-allergic pharmaceutical composition, there is inadequate written description about the structure associated with function of all allergen without the amino acid sequence in the claimed composition. Likewise, the polynucleotide encoding all allergen in the claimed composition is not adequately described. Adequate written description requires more than a mere statement that it is part of the invention. The amino acid sequence itself for the allergen and/or the nucleic acid itself for the allergen are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

With regard to claims 49-50, the term "of sequence" could be open or close ended. There is inadequate written description about the amino acids to be added to the peptide.

With regard to claim 55, the term "at least one" means there are one or more than one polynucleotide encoding the allergen comprises a sequence SEQ ID NO: 1. The specification as filed does not disclose a polynucleotide encoding any allergen, let alone the other polynucleotide encoding the allergen.

With regard to claims 56-57, SEQ ID NO: 6 in claim 56 and SEQ ID NO: 7 in claim 57 are primers. Primers do not encode the allergen.

Finally, the specification discloses only one allergen from *D. Pteronyssinus* and one inhibitor of histamine synthesis, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of allergens, polynucleotide encoding all allergen and inhibitor of histamine synthesis to describe the genus for the claimed composition. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. Claims 36-63 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "An anti-allergic pharmaceutical composition, comprising: (i) an antihistamine compound, (ii) an inhibitor of histamine synthesis and **optionally, (iii) an allergen or an isolated nucleic acid molecule comprising at least one polynucleotide sequence encoding said allergen**, and said antihistamine compound, inhibitor, and optional allergen or isolated nucleic acid molecule being combined in said composition with a pharmaceutically acceptable carrier" in claim 36 represents a departure from the specification and the claims as originally filed. The passages pointed out by applicant in the amendment filed 9/1/04 do not provide a clear support for the said phrase. The specification discloses only an anti-allergic pharmaceutical composition contains (i) at least one allergen and (ii) at least one antihistamine compound and optionally (iii) at least one inhibitor of histamine synthesis in a pharmaceutically acceptable vehicle (page 5). The claim as written now the allergen is optional. Further, the composition optionally comprises any polynucleotide sequence encoding any allergen.

The "... isolated nucleic acid molecule comprises at least one polynucleotide sequence encoding said allergen is an adenoviral vector" in claim 54 represents a departure from the specification and the claims as originally filed. The passages pointed out by applicant in the amendment filed 9/1/04 do not provide a clear support for the said phrase.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

14. Claims 54 and 56-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "...isolated nucleic acid molecule comprises at least one polynucleotide sequence encoding said allergen **is** an adenoviral vector" in claim 54 is indefinite and ambiguous because the adenoviral vector is NOT the polynucleotide sequence encoding said allergen. The isolated nucleic molecule comprises at least one polynucleotide sequence encoding said allergen is in an adenoviral vector or an adenoviral vector comprises the isolated nucleic acid molecule encoding said allergen.

The "...comprises a nucleotide sequence corresponding to the sequence of SEQ ID NO: 6" in claim 56 is indefinite and ambiguous because SEQ ID NO: 6 is a primer and not the polynucleotide encoding said allergen.

Likewise, the "...comprises a nucleotide sequence corresponding to the sequence of SEQ ID NO: 7" in claim 57 is indefinite and ambiguous because SEQ ID NO: 7 is a primer and not the polynucleotide encoding said allergen. SEQ ID NO: 6 and 7 are primers.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claim 36, 39, 42-43, and 59-63 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,256,680 (Oct 1993; PTO 892).

The '680 patent teaches an anti-allergic pharmaceutical composition comprising an inhibitor of histamine synthesis, which is also a histidine decarboxylase inhibitor such as α-fluoromethyhistidine combined with one or more antihistamine compound such as H1 or H2 receptor antagonist such as cimetidine, ranitidine, terfenadine, famotidine (see col. 11, lines 33-45, in particular). The term comprising is open-ended. It expands the claimed composition to include additional compound to include the reference composition. The reference composition inherently has the same anti-allergic response given the ingredients in the claimed composition

has the same ingredient and is for treating allergic disease (see col. 3, line 46-47, in particular). The reference composition comprising the reference inhibitor of histamine synthesis or histidine decarboxylase inhibitor is present from 0.5 to 50mg or 1 mg to 10mg which is between claimed range of 1 and 2000 or between 5 and 200 mg (see col. 6, lines 23-35, in particular). The reference composition is releasable in the mucosal form such as buccal administration, nasal administration that is known to skilled in the art of pharmacy (see col. 6, line 59-67, in particular). Thus, the reference teachings anticipate the claimed invention.

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 36-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,256,680 (Oct 1993; PTO 892) in view of US Pat No 4,302,458 (of record, Nov 1981, PTO 892) and US Pat No 6,258,816 (of record, July 2001, PTO 892) or US Pat No. 5,827,852 (of record, Oct 1998, PTO 892) or US Pat No 6,319,513 (of record, Nov 2001, PTO 892).

The teachings of the '680 patent have been discussed supra.

The claimed invention as recited in claim 37 differs from the teachings of the reference only in that the pharmaceutical composition further comprising more than one antihistamine compound and more than one inhibitor of histamine synthesis.

The claimed invention as recited in claim 38 differs from the teachings of the reference only in that the pharmaceutical composition wherein the antihistamine compound is

brompheniramine, cetirizine, fexofenadine, cyproheptadine, dexchlorpheniramine, hydroxyzine, ketotifen, loratidine, mequitazine, oxotomide, mizolastine, ebastine, astemizole, carbinoxamide, alimemazine, buclizine, cyclizine, hydrochlorate, and doxylamine.

The claimed invention in claim 40 differs from the teachings of the reference only in that the pharmaceutical composition wherein the inhibitor of histamine synthesis is an inhibitor of histidine decarboxylase is tritoqualine.

The claimed invention as recited in claim 41 differs from the teachings of the reference only in that the pharmaceutical composition wherein the antihistamine compound is present in an amount between 1 and 2000 mg.

The claimed invention as recited in claim 42 differs from the teachings of the reference only in that the pharmaceutical composition wherein the antihistamine compound is present in an amount between 5 and 200 mg.

The claimed invention as recited in claim 43 differs from the teachings of the reference only in that the pharmaceutical composition wherein the inhibitor of histamine synthesis is present in an amount between 1 and 2000 mg.

The claimed invention as recited in claim 44 differs from the teachings of the reference only in that the pharmaceutical composition wherein the inhibitor of histamine synthesis has from 5 to 200 mg of antihistamine and from 10 to 300 mg of a histidine decarboxylase inhibitor.

The '458 patent teaches a pharmaceutical composition comprising tritoqualine which has been known for its anti-allergy properties and its derivative such as 458 L (See column 1, lines 11-13, in particular). The reference tritoqualine and 458 L are histamine decarboxylase inhibitors (See column 5, lines 3-10, Table, in particular) and are useful in treatment of allergy conditions such as pollinoses, uriticaria, eczema (See column 5, lines 30-33, claims 7-9, in particular). The '458 patent further teaches that the reference pharmaceutical composition can be administered orally, rectally, in a daily dosage of 20 to 500 mg and in the forms of tablets, pills, or suppositories wherein the reference dosage is within the claimed dosage of between 1 and 2000 mg, or within the claimed dosage of from 5 to 200 mg (See column 5, lines 34-37, in particular).

The '816 patent teaches anti-allergy anti-inflammatory composition comprising an antihistamine such as cetrizine at a dose of 1.16mg/kg and an anti-leukotriene such as Nimesulide for asthma (See claims 1-6 of '816 patent, in particular). The '816 patent teaches various Histamine receptor antagonist such as cetirizine, fexofenadine, acrivastine, asthmizole, and loratidine for treatment of allergic rhinitis as they are long acting and are free from sedative and

anticholinergic effects (See column 4, lines 43-47, in particular). The '816 patent further teaches that cetirizine is very effective in inhibiting the cutaneous early and late phase response by inhibiting PAF and eosinophil recruitment in skin (See column 5, line 3-5, in particular).

The '852 patent teaches various pharmaceutical composition comprising various sedating antihistamine such as chlorpheniramine, brompheniramine dexchlorpheiramine, cyproheptadine, hydroxyzine, and various non-sedating antihistamine such as ketotifen, loratidine, oxatomide, astemizole, and ebastine for treating allergy (See summary of Invention, column 6, lines 5-20, claims 1, and 6-12 of '852 patent, in particular).

The '513 patent teaches various pharmaceutical composition comprising various sedating antihistamine and non-sedating antihistamines such as dexchlorpheniramine, cyproheptadine, fexofeadine, loratidine, ebastine, astemizole, hydrozyzine (See column 10, lines 55 bridging column 11, lines 1-2, in particular). The '513 patent teaches that the reference composition is administered usually from 0.5 mg/kg to about 500 mg/kg per day, which is equivalent to 25 mg to 50 mg for an average person of 50 kg. The '513 patent teaches that the reference composition is administered from about 1 mg/kg to about 300 mg/kg per day, which is equivalent to 50 mg to 15000 mg or preferably from about 5 mg/kg per day to about 200 mg/kg per day, which is equivalent to 250 to 10,000 mg per day (See column 16, lines 23-31, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the histidine decarboxylase inhibitor such as α-fluoromethyhistidine and antihistamine compound such as H1 or H2 receptor antagonist such as cimetidine as taught by the '680 patent for the tritoqualine, which is also a histidine decarboxylase inhibitor as taught by the '458 patent and/or to substitute the antihistamine compound such as H1 or H2 receptor antagonist such as cimetidine as taught by the '680 patent for the various antihistamine compound such as cetirizine, fexofenadine, acrivastine, asthmizole, and loratidine taught by the '816 patent, or the chlorpheniramine, brompheniramine dexchlorpheiramine, cyproheptadine, hydroxyzine, and various non-sedating antihistamine such as ketotifen, loratidine, oxatomide, astemizole, and ebastine taught by the '852 patent and '513 patent in an anti-allergic pharmaceutical composition comprising any antihistamine compound and any histidine decarboxylase inhibitor as taught by the '680 patent, the '816 patent, the '852 patent and '513 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '458 patent teaches tritoqualine and 458 L are histamine decarboxylase inhibitor (See column 5, lines 3-10, Table, in particular) and they are useful in treatment of allergy conditions such as pollinoses, uriticaria, eczema (See column 5, lines 30-33, claims 7-9, in particular). The '816 patent teaches that histamine receptor antagonist such as cetirizine, fexofenadine, acrivastine, asthmizole, and loratidine for treatment of allergic rhinitis as they are long acting and are free from sedative and anticholinergic effects (See column 4, lines 43-47, in particular) and that cetirizine is very effective in inhibiting the cutaneous early and late phase response by inhibiting PAF and eosinophil recruitment in skin (See column 5, line 3-5, in particular). The '852 patent teaches that various sedating antihistamine such as chlorpheniramine, brompheniramine dexchlorpheiramine, cyproheptadine, hydroxyzine, and various non-sedating antihistamine such as ketotifen, loratidine, oxatomide, astemizole, and ebastine are useful for treating allergy (See summary of Invention, column 6, lines 5-20, claims 1, and 6-12 of '852 patent, in particular). The '680 patent teaches an anti-allergic pharmaceutical composition comprising an inhibitor of histamine synthesis, which is also a histidine decarboxylase inhibitor such as α-fluoromethyhistidine combined with one or more antihistamine compound such as H1 or H2 receptor antagonist such as cimetidine, ranitidine, terfenadine, famotidine (see col. 11, lines 33-45, in particular) and are useful for treating allergic diseases (see col. 3, line 46-47, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06). In re Aller, 220 F2d 454,456,105 USPQ233; 235 (CCPA 1955). See MPEP § 2144.05 part IIA. Therefore, the claimed invention is an obvious variation of the reference teachings, absent a showing of unobvious differences.

20. Claims 36, 39, 45-53, 55, and 58-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,256,680 (Oct 1993; PTO 892) in view of US Pat No 6,455,686 (Sept 2002, PTO 892) or US Pat No 5,433,948 (July 1995; PTO 892) or US Pat No 5,820,862 (Oct 1998; PTO 892).

The teachings of the '680 patent have been discussed supra.

The claimed invention in claim 36 differs from the teachings of the reference only in that the pharmaceutical composition comprises optionally an allergen.

The claimed invention in claim 45 differs from the teachings of the reference only in that the anti-allergic pharmaceutical composition wherein said allergen is chosen from the major antigens or a mixture of major antigens of acarids, capable of inducing an immune reaction.

The claimed invention in claim 46 differs from the teachings of the reference only in that the anti-allergic pharmaceutical composition wherein said allergen is a major antigen of *D. Pteronyssinus* and/or *D. Farinae*.

The claimed invention in claim 47 differs from the teachings of the reference only in that the anti-allergic pharmaceutical composition wherein said allergen is a cystine protease.

The claimed invention in claim 48 differs from the teachings of the reference only in that the anti-allergic pharmaceutical composition wherein said allergen is at least one peptide epitope of a cystine protease.

The claimed invention in claim 49 differs from the teachings of the reference only in that the anti-allergic pharmaceutical composition wherein said allergen is at least one peptide epitope of a cystine protease of sequence SEQ ID NO: 2.

The claimed invention in claim 50 differs from the teachings of the reference only in that the anti-allergic pharmaceutical composition wherein said allergen is a peptide or a mixture of peptides chosen from the group consisting of the peptides of sequences SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5.

The claimed invention in claim 51 differs from the teachings of the reference only in that the anti-allergic pharmaceutical composition wherein said allergen is natural and is obtained by extraction of the acarids *D. Pteronyssinus* and/or *D. Farinae*.

The claimed invention in claim 52 differs from the teachings of the reference only in that the anti-allergic pharmaceutical composition wherein said allergen is present in an mount of 1 to 1500 μg.

The claimed invention in claim 53 differs from the teachings of the reference only in that the anti-allergic pharmaceutical composition wherein said allergen is present in an amount of 10 to 150 μg.

The claimed invention in claim 55 differs from the teachings of the reference only in that the anti-allergic pharmaceutical composition wherein said allergen is at least one polynucleotide sequence encoding said allergen comprises a sequence SEQ ID NO: 1.

The claimed invention in claim 59 differs from the teachings of the reference only in that the pharmaceutical composition is releasable in mucosal form, in the form of an eye lotion, in the form of a nasal spray or in bronchial form.

The claimed invention in claim 60 differs from the teachings of the reference only in that the pharmaceutical composition is releasable in a pharmaceutical form for programmed disintegration mucosally or sublingually and secondarily per os.

The '686 patent teaches an anti-allergic pharmaceutical composition comprising an allergen such as high molecular weight *Dermatophagoides farinae* proteins from mite in conjunction with other compound such as anti-histamines (column 42, lines 40-59, in particular) associated with a pharmaceutical acceptable vehicle such as phosphate buffered saline (PBS, see column 44, line 63 bridging column 45, line 1, in particular) in a controlled released formulation such as liposome, transdermal delivery systems, or osmotic pumps (See column 41, lines 20-33, in particular). The reference whole dust mite allergen from *Dermatophagoides farinae* inherently contains the major antigens of acrid which is capable of induce an immune reaction such as immediate hypersensitivity response (See column 51, Table 2, lines 13-15, in particular). The reference pharmaceutical composition contains from about 0.5 ng to about 1 g per kg body weight (See column 42, lines 26-28, in particular). The '686 patent further teaches a composition comprising anti-inflammatory agent or compound such as peptides from IgE or IgE specific Fc receptors or antibodies capable of binding to IgE and blocks IgE binding to Fc receptors that drive immunoglobulin heavy class switching from IgE to IgG which inherently switch from Th2 to Th1 that reduce IgE synthesis in the upstream phase while the reference anti-histamine inhibits the histamine release in the down stream phase (See column 42, lines 45-49, in particular). The reference pharmaceutical composition is administered in form of subcutaneous, intradermal, intravenous, nasal, oral, transdermal in the form of transcutanous patch and intramuscular routes (See column 42, lines 35-39, in particular). The reference pharmaceutical composition is useful to treat allergic hypersensitivity reactions to dust mite such as allergic asthma, allergic rhinitis, atopic and allergic eczema or to desensitize humans who are allergic to dust mite (See column 36, lines 31-36, column 42, lines 60-63, in particular). The reference pharmaceutical composition contains a quantity of 1 x 10^{-8} microgram to about 100 μg or from about 1x 10^{-7} μg to about 10 μg (See column 27, lines 31-34, in particular). Claim 14 is included in this rejection because the claimed limitations of 1 to 1500 μg or from 10 to 150 μg include the reference quantity of allergy.

The '948 patent teaches an anti-allergic pharmaceutical composition comprising various allergens such as *D. farinae* allergen comprises the amino acid sequence of SEQ ID NO: 2 and encoded by the polynucleotide sequence comprises SEQ ID NO: 1. The reference polypeptide is 100% identical to the claimed SEQ ID NO: 2 wherein the reference allergen obvious has at least one epitope of a cystine protease (see summary of invention, col. 5, lines 35-53, col. 7, lines 25-37, in particular). The reference *D. farinae* allergen is a cystine protease (see col. 7, lines 25-37, in particular). The reference allergen is useful as common immunotherapeutic peptides for treating allergy because two or more mite species share the epitope (see col. 10, lines 26-35, in particular).

The '862 patent teaches an anti-allergic pharmaceutical composition comprising various allergens such as *D. Pteronyssinus* and *D. Farinae* or combination of peptides from *D. Pteronyssinus* and *D. Farinae* for treatment of allergy (see entire document, abstract, summary of invention, in particular). The '862 patent teaches various T cell epitopes (peptide) from *D. Pteronyssinus* and *D. Farinae* and mixture of peptides comprises SEQ ID NO: 10, 23 and 40. The reference peptides of SEQ ID NO: 10, 23 and 40 contain the claimed peptide of SEQ ID NO: 3, SEQ ID: 4 and SEQ ID NO: 5, respectively. The reference pharmaceutical composition is administered by subcutaneous injection, transdermal application, oral administration (mucosal), inhalation (nasal spray) (see col. 16, lines 42-55, in particular). The reference composition wherein the allergen is present in an amount of about 20-500 μg (see col. 16, lines 60-63, in particular) which is within the claimed amount of 1 to 1500 μg. The reference about 20 μg is within the claimed range of 10 to 150 μg. The '862 patent also teaches polynucleotide sequence such as SEQ ID NO: 1 that that encodes the reference allergen comprises SEQ ID NO: 2 (see reference SEQ ID NO: 1, in particular). Claims 56 and 57 are included in this rejection because the term "comprises" is open-ended. It expands the primers of SEQ ID NO: 6 and 7 to include additional nucleotide at either or both ends to include the reference polynucleotide. The '862 patent further teaches isolated nucleic acid molecule encoding the reference allergen in various vector such as pMSG vector (see col. 8, lines 67, in particular)pTRC vector (see col. 9, lines 3-39, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the anti-allergic pharmaceutical composition comprising an inhibitor of histamine synthesis such as α-fluoromethyhistidine, with one or more antihistamine compound such as H1 or H2 receptor antagonist such as cimetidine, ranitidine, terfenadine,

famotidine as taught by the '680 patent with the allergen Dermatophagoides farinae proteins from mite as taught by the '686 patent or the allergen from mite such as *D. farinae* allergen comprises the amino acid sequence of SEQ ID NO: 2 as taught by the '948 patent or the various allergens such as *D. Pteronyssinus* and *D. Farinae* or combination of peptides from *D. Pteronyssinus* and *D. Farinae* as taught by the '860 patent for treatment allergy as taught by the '680 patent, the '686 patent, the '948 patent and the '860 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to combine because The '680 patent teaches the combination of inhibitor of histamine synthesis, which is also a histidine decarboxylase inhibitor such as α-fluoromethyhistidine and one or more antihistamine compound such as H1 or H2 receptor antagonist such as cimetidine, ranitidine, terfenadine, famotidine are useful for treating allergic diseases (see col. 3, line 46-47, in particular). The '686 patent teaches the combination of allergen from *Dermatophagoides farinae* and anti-histamines are useful for treating allergic hypersensitivity reactions to dust mite such as allergic asthma, allergic rhinitis, atopic and allergic eczema or to desensitize humans who are allergic to dust mite (See column 36, lines 31-36, column 42, lines 60-63, in particular). The '948 patent teaches allergen such as *D. farinae* allergen comprises the amino acid sequence of SEQ ID NO: 2 that encoded by the polynucleotide sequence comprises SEQ ID NO: 1 is useful for treating allergy to the two or more mite species which share the same epitope (see col. 10, lines 26-35, in particular). The '862 patent teaches allergens such as *D. Pteronyssinus* and *D. Farinae* or combination of peptides from *D. Pteronyssinus* and *D. Farinae* are useful for treating allergy (see entire document, abstract, summary of invention, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

21. Claims 54 and 56-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,256,680 (Oct 1993; PTO 892) in view of US Pat No 6,455,686 (filed April 1999, PTO 892) or US Pat No 5,433,948 (July 1995; PTO 892) or US Pat No 5,820,862 (Oct 1998; PTO 892) as applied to claims 36, 39, 45-53, and 59-63 mentioned above and further in view of Hsu et al (Int

Immunol 8(9): 1405-11, Sept 1996; PTO 892), Ginkel et al (J Immunol 159(2): 685-93, July 1997; PTO 892) and Hoyne *et al* (Immunology and Cell Biology 74: 180-186, 1996, PTO 892).

The combined teachings of '680, the '686, the '948, and '862 patents have been discussed supra. The '862 patent further teaches polynucleotide sequence such as SEQ ID NO: 1 that that encodes the reference allergen comprises SEQ ID NO: 2 (see reference SEQ ID NO: 1, in particular). Claims 56 and 57 are included in this rejection because the term "comprises" is open-ended. It expands the claimed oligonucleotide of SEQ ID NO: 6 and 7 to include additional nucleotide at either or both ends to include the reference polynucleotide.

The claimed invention as recited in claim 54 differs from the teachings of the combined references only in that the pharmaceutical composition wherein the nucleic acid molecule comprises at least one polynucleotide sequence encoding the allergen is an adenoviral vector.

The claimed invention as recited in claim 55 differs from the teachings of the combined reference only in that the pharmaceutical composition wherein said at least one polynucleotide sequence encoding said allergen comprises a sequence of SEQ ID NO: 1.

The claimed invention as recited in claim 56 differs from the teachings of the combined reference only in that the pharmaceutical composition wherein said at least one polynucleotide sequence encoding said allergen comprises a nucleotide sequence corresponding to the sequence of SEQ ID NO: 6.

The claimed invention as recited in claim 57 differs from the teachings of the combined reference only in that the pharmaceutical composition wherein said at least one polynucleotide sequence encoding said allergen comprises a nucleotide sequence corresponding to the sequence of SEQ ID NO: 7.

Hsu et al teach administering gene construct such as CMVD vector containing the polynucleotide of *D. pteronyssium* resulted in allergen specific reduction of IgE and high level of interferon gamma (Th 1 immune response) which probably inhibit allergen specific immune responses (see abstract, in particular). The reference DNA immunization is an attractive approach in altering the host immune response to allergen (see entire document, abstract, in particular).

Ginkel et al teach the use of replication deficient adenovirus vectors comprising the polynucleotide of interest as mucosal vaccine and adenovirus vectors are effective to specifically target to the respiratory epithelium (see abstract, in particular). Ginkel et al teach adenoviral gene

delivery of antigen such as βgal elicits βgal specific interferon gamma (IFNγ), which is a Th1 response 9 (see page 692, col. 1, last paragraph, in particular).

Hoyne *et al.* teach patients receiving the PLA-2 specific peptides from bee venom demonstrated a decrease in allergen specific IgE and a corresponding rise in IgG levels; most patients reported a significant improvement in clinical symptoms (See page 183, column 1, paragraph 2, in particular). Hoyne *et al.* further teach peptide-mediated regulation of allergic immune response and a successful desensitization using peptide-mediated immunotherapy is accompanied by a decrease Th2-type cytokine with a concomitant increase in IFNγ production (See page 180, column 2, in particular). The reference further teaches that the key to successful immunotherapy may dependent on reprogramming the immune response by co-administering allergen peptide in the presence of IL-12 or IFNγ or immunizing with recombinant live vaccine vectors such as mycobacteria expressing defined allergens or fragments (See page 183, column 2, paragraph 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the vector comprising the polynucleotide of SEQ ID NO: 1 as taught by the '860 patent or the CMV vector that contains the polynucleotide that encodes the *D. pteronyssium* allergen as taught by Hsu et al for the adenoviral vector as taught by Ginkel et al for an anti-allergic pharmaceutical composition comprising an adenoviral vector that contains the polynucleotide that encodes either the *D. pteronyssium* or *D. Farinae* allergen as taught by the '680, the '686, the '948, and '860 patents, Ginkel et al and Hsu et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Hsu et al teach that immunizing polynucleotide encoding the allergen of interest in a vector is an attractive approach in inducing Th1 host immune response to allergen (see entire document, abstract, in particular). Ginkel et al teach adenoviral gene delivery of any antigen of interest elicits antigen specific interferon gamma (IFNγ), which is a Th1 response 9 (see page 692, col. 1, last paragraph, in particular). Hoyne *et al.* teach successful desensitization using peptide-mediated immunotherapy is accompanied by a decrease Th2-type cytokine with a concomitant increase in IFNγ production (See page 180, column 2, in particular).

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

24. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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